CYCLOSPORIN-CONTAINING SOFT CAPSULE COMPOSITIONS

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a soft capsule composition containing a stable microemulsion concentrate which is more stable and suitable for the preparation of cyclosporin-containing soft capsules. More specifically, the present invention relates to a microemulsion concentrate containing cyclosporin as an active ingredient, polyethylene glycol as a cosurfactant, one component or a mixture of two or more selected from the group consisting of an esterified compound of fatty acid and primary alcohol, medium chain fatty acid triglyceride and monoglyceride as an oil component, and a surfactant having HLB value of 10 to 17 such as Nikkol HCO-50 or Tween 20, which is suitable for formulation into soft capsules and to a soft capsule composition containing said microemulsion concentrate.

2. Background Art

Cyclosporin is a specific macromolecular (molecular weight 1202.64) cyclic peptide compound consisting of 11 amino acids, which has broad spectrum of useful pharmacological activities, particularly immuno-suppressive activity and anti-inflammatory activity. Therefore, cyclosporin has been used for suppression of inherent immunological responses of the living body, which are caused by tissue and organ transplantation, for example, transplantation of the heart, lung, liver, kidney, pancreas, bone marrow, skin and cornea, and especially the transplantation of foreign tissues and organs. In addition, cyclosporin is useful for the suppression of hematological disorders such as anemia, various autoimmune diseases such as systemic lupus erythematosus, idiopathic malabsorption syndrom, etc., and inflammatory diseases such as arthritis, rheumatoid disorder, etc. Cyclosporin is also useful in treatment of protozoal diseases such as malaria, schistosomiasis, etc., and furthermore, recently it is partly used in chemotherapy.

Cyclosporin is highly lipophilic and hydrophobic with a solubility in water at 25° C. being 16 to 23 mg of cyclosporin per liter of water. On the other hand, cyclosporin is well dissolved in an organic solvent such as methanol, ethanol, acetone, ether, chloroform and the like, due to its high lipophilic property. Due to low water-solubility of cyclosporin having above mentioned properties, when cyclosporin is administered per oral, its bioavailability is extremely low and may be greately influenced by the condition of each individual patient. Accordingly, it is very difficult to retain an effective therapeutic concentration. Moreover, cyclosporin may shows considerable side effects such as nephrotoxicity. Thus, cyclosporin is very difficult to formulate into a preparation for oral administration due to its low water solubility. Accordingly, numerous studies have been extensively conducted to find a preparation suitable for the effective oral administration of cyclosporin, which can provide a suitable uniform dosage and appropriate bioavailability.

The prior art preparations suitable for oral administration of sparingly water-soluble cyclosporin are usually formulated in the form of a microemulsion by combining cyclosporin with a surfactant, an oil and a cosurfactant.

One typical method using this combination is taught in U.S. Pat. No. 4,388,307 which is issued on Jun. 14, 1983. This patent discloses a liquid formulation of cyclosporin using ethanol as a cosurfactant. According to the method

disclosed in this U.S. Patent Specification, cyclosporin is combined with a carrier consisting of ethanol as a cosurfactant, olive oil as a vegetable oil, and a transesterification product of a natural vegetable oil triglyceride and a polyalkylene polyol as a surfactant to form the liquid formulation. However, the resulting liquid formulation is administered as an aqueous dilution which makes it very difficult to adapt the subject to its administration and to provide a uniform dosage for oral administration.

In order to mitigate the inconvenience of diluting the cyclosporin liquid composition in water prior to oral administration, a liquid composition in the form of a microemulsion concentrate has been formulated into a soft capsule preparation, which is now commercially available as Sandimmun® (trademark). In this preparation, the cyclosporin soft capsule contains a large amount of ethanol as a cosurfactant due to the solubility requirements of cyclosporin. However, since ethanol, which has a low boiling point, permeates the gelatin membrane of the capsule to volatilize even at normal temperature, the content of ethanol is reduced and the constitutional ratio of the contents in soft capsules varies during storage. The reduced ethanol content results in crystallization of cyclosporin and a significant difference in the bioavailability of cyclosporin. Thus, it make the determination of dosage of cyclosporin which can provide a suitable therapeutic effect difficult.

In an effort to prevent the volatilization of ethanol from the soft capsule preparations during storage and distribution, the soft capsule preparations are wrapped in a special packing material, such as an aluminum film foam package. However, such specific packaging does not completely maintain the uniform composition of the wrapped capsule. It has been demonstrated through experiments that although the cyclosporin soft capsule is wrapped up in aluminum film foam package, the ethanol content is lowered to 7.9% from the initial level of 10.8% after a period of one week. This results in a great difference in bioavailability of cyclosporin and may contribute to the price increase.

To solve the above-mentioned disadvantages which accompany the use of ethanol as a cosurfactant, a method using a non-ethanol component as a cosurfactant has been proposed. For example, British Laid-open Patent Publication No. 2,228,198 (Feb. 16, 1990) discloses a method for increasing stability and bioavailability of cyclosporin preparations by containing a vegetable oil triglyceride of saturated fatty acid such as caprylic/capric acid triglyceride [trade mark: MIGLYOL 812] or linolenic acid monoglyceride [trade mark: MYVEROL 18-92] as an oil component and a surfactant having HLB (Hydrophilic-lipophilic balance) value of 10 or more, particularly a reaction product of castor oil and ethylene oxide [trade mark: CREMOPHOR RH 40]. In addition, Korean Laid-open Patent Publication No. 90-4348 (Apr. 12, 1990) discloses a pharmaceutical composition in the form of a microemulsion concentrate containing a non-ethanol component which is selected from pharmaceutically acceptable C_{1-5} alkyl or tetrahydrofurfuryl di- or partial-ether of low molecular mono- or poly-oxyalkanediol, for example, diethyleneglycol monoethyl ether [trade mark: TRANSCUTOL] or tetrahydrofurfuryl alcohol polyethylene glycol [trade mark: GLYCOFUROL] and 1,2-propyleneglycol as a cosurfactant, a medium chain fatty acid triglyceride, particularly caprylic/capric acid triglyceride [trade mark: MIGLYOL 812], as an oil component, and a reaction product of castor oil and ethylene oxide [trade mark: CREMOPHOR RH 40] as a surfactant. Such soft capsule formulations result in somewhat increasing in bioavailability of cyclosporin in comparison with prior com-